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Variability of Cardiac Electromechanical Delay With Application to the Noninvasive Detection of Coronary Artery Disease

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ABSTRACT Heart rate variability (HRV), systolic period variability (SPV), and diastolic period variability (DPV) have shown potential for assessing cardiac function. It is unknown whether the time delay between the myocardial electrical and mechanical activities (i.e., electromechanical delay, EMD) also possesses variability, and if it does, whether this EMD variability (EMDV) could render additional value for cardiac function assessment. In this paper, we extracted the beat-to-beat EMD from 5-min simultaneously recorded electrocardiogram and phonocardiogram signals in 30 patients with coronary artery disease (CAD) and 30 healthy control subjects, and studied its variability using the same methods as applied for HRV including time-domain measures [mean and standard deviation (SD)], frequency-domain measures [normalized low- and high-frequency (LFn, HFn) and LF/HF)], and nonlinear measures [sample entropy (SampEn), permutation entropy (PE), and dynamical patterns]. In addition, we examined whether the addition of EMDV could offer improved performance for distinguishing between the two groups compared to using the HRV, SPV, and DPV features. Support vector machine with 10-fold cross-validation was used for classification. Results showed increased SD of SPV, increased mean, SD and decreased SampEn of EMDV in CAD patients. Besides, the dynamical pattern analysis showed that CAD patients had significantly increased fluctuated patterns and decreased monotonous patterns in EMDV. In particular, the addition of EMDV indices dramatically increased the classification accuracy from 0.729 based on HRV, SPV, and DPV features to 0.958. Our results suggest promising of the EMDV analysis that could potentially be helpful for detecting CAD noninvasively.

INDEX TERMS Electromechanical delay (EMD), heart rate variability (HRV), systolic period variability (SPV), diastolic period variability (DPV), dynamical patterns, noninvasive detection, coronary artery disease (CAD).

I. INTRODUCTION

Electrocardiogram (ECG) and phonocardiogram (PCG) measurements are two commonly-used non-invasive and non-intrusive methods for diagnosing cardiac diseases. ECG reflects the cardiac electrical activity while PCG records heart sounds produced by myocardial mechanical activities (i.e., contraction and relaxation). One cardiac cycle is composed of two mechanical intervals, namely, systolic period (SP) and diastolic period (DP). Previous studies have found reduced mean cardiac cycle (i.e., mean RR intervals in ECG) in diabetes [1] and patients with chronic congestive heart failure [2]. Besides, researchers also found that abnormal SP and DP could indicate mechanical abnormalities of ventricular function [3]. Prolonged SP and shortened DP were found in children with heart failure [4], [5], and the shortening

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of DP was also found in spontaneous angina [6], dilated cardiomyopathy [7], and exercise-induced increased pulmonary artery pressure [8]. In addition to these well-studied cardiac electrical and mechanical time intervals, there is yet another time interval characterizing the delay between the onset of the electrical activation of the ventricle and the onset of its contraction—the electro-mechanical delay (EMD) [9], [10]. Previous studies have observed increased EMD in patients with heart failure [10] and in athletes after road races [11].

Besides the mean levels of RR, DP, and SP, researchers have also well documented their variations from one cardiac cycle to another, namely heart rate variability (HRV), diastolic period variability (DPV), and systolic period variability (SPV) [12], [13]. It is generally accepted that HRV originates from the spontaneous activity of the sinoatrial node and the regulation of autonomic nervous system [14]. Decreased HRV has been found in patients with various cardiovascular diseases (e.g. myocardial infarction [15], congestive heart failure [16], and idiopathic dilated cardiomyopathy [17]). Altered physiological states could also lead to HRV changes [18]–[21]. The existing of DPV and SPV is presumably as a result of HRV [13] but a recent study has also showed that they might possess intrinsic variations [22]. Both SPV and DPV increased significantly after exercise [13]. Decreased DPV was significantly associated with aging in healthy subjects [23] and was found in patients with congestive heart failure [22]. However, to the best of our knowledge, little is known whether there are also beat-to-beat variations in the EMD time-series, and whether this EMD variability (EMDV), if there is, render valuable information about disease or physiological changes.

In the current study, we sought to elucidate this EMDV in both healthy subjects and patients with coronary artery disease (CAD) in comparison with HRV, DPV, and SPV. To study the EMDV, we applied the same approaches including time- and frequency-domain features as well as nonlinear measures as used for HRV analysis in previous literatures. To validate the value of EMDV for CAD detection, we fitted separately two support vector machine (SVM) classifiers without and with EMDV features and evaluated the performance in terms of accuracy, sensitivity, specificity, F-1 score, and the area under the receiver operating characteristic curve (AUC). Details on the study design and subjects, data collection, constructions of time-series, analyzing methods, and statistical methods were illustrated in Section II. Results were presented in Section III followed by discussions in Section IV. A short conclusion was provided in Section V.

II. METHOD

A. SUBJECTS AND DATA COLLECTION

Thirty CAD patients and 30 age- and gender-matched healthy volunteers participated in this study. Health status for the healthy volunteers were confirmed by routine ECG, echocardiography, arterial function, and routine biochemical examinations. Inclusion criterion for CAD patients was $\geqq$ 50% stenosis in at least one branch of left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA) according to the coronary angiography. Patients who had undergone coronary artery bypass surgery or percutaneous coronary intervention (PCI) were excluded before participation. Baseline characteristics of all subjects were summarized in Table 1. The study has obtained approval from the Institutional Review Board of Shandong Provincial Qianfoshan Hospital. All subjects were instructed carefully about this study and gave their informed consents before participation.

TABLE 1. Baseline characteristics of subjects.

	Healthy group	CAD group	*p* value
No. (Male/Female)	30 (16/14)	30 (18/12)	0.60
Age, years	56±8	58±8	0.43
BMI, kg/m2	24±8	26±3	0.41
SBP, mmHg	114±13	117±14	0.19
DBP, mmHg	72±9	74±9	0.23
LVEF, %	65±4	61±6	0.30

Data are expressed as number (male/female) or mean ± standard deviation.

Abbreviation: BMI = Body mass index, SBP = Systolic blood pressure, DBP = Systolic blood pressure; LVEF = Left ventricular ejection fraction.

A Cardiovascular Function Detection device (CV FD–II, Jinan Huiyironggong Tech. Co. Ltd., P. R. China) was used for data collection. Prior to formal recording, all subjects were required to lie in supine position on a measurement bed for at least 15 min in a quiet and temperature-controlled room (25 ± 3 °C). The standard lead-II configuration was used for ECG recording. In the meantime, a piezoelectric sensor placed on the left sternal border in the third intercostal space was used to simultaneously collect heart sound (i.e., PCG). Both recordings were simultaneously recorded for 5 min at a sampling rate of 1,000 Hz.

B. CONSTRUCTION OF CARDIAC ELECTROMECHANICAL TIME-SERIES

The diagnostic useful frequency ranges of ECG and PCG are usually accepted as 0.05-75Hz [24] and 25-250Hz [25], respectively. Therefore, all raw signals were first bandpass filtered with second-order Butterworth filters with the passband of 0.05-75 Hz for ECG and 25-250 Hz for PCG followed by band-stop filtering to remove the power interference (50 Hz) [26], [27]. Quality of ECG and PCG was inspected visually side-by-side and episodes with poor quality were marked. If the combined percentage of episodes identified with poor quality for each subject went beyond 10%, the recordings would be considered invalid and the subject would be excluded. Then a template-matching algorithm was used to automatically extract R-wave peaks of ECGs [28]. The fore-and-aft R-wave positions formed the raw RR interval time-series. Anomalous RR intervals due to

ectopic beats (such as premature supraventricular or ventricular contractions) were eliminated from the raw RR interval time series [29]. QRS onset (i.e., Q-onset) corresponding to each R-wave peak was identified manually. Besides, in each cardiac cycle, the mitral component (M1) of the first heart sound (i.e., S1) and the aortic component (A2) of the second heart sound (i.e., S2) were identified manually with the R-wave peak as a reference. SP time series were constructed by intervals between M1 and A2 in the same cardiac cycle while DP time series were constructed by intervals between A2 and M1 of the following cardiac cycle. Finally, the interval between Q-onset of ECG and M1 of PCG in the same cardiac cycle was defined as EMD. All the corresponding intervals in SP, DP, and EMD time-series were also removed if the RR interval was considered anomalous. If the combined percentage of anomalous intervals identified for each subject was $>10\%$, the subject would be excluded from further analysis, too. The construction of RR, SP, DP, and EMD time-series was illustrated in Fig. 1. Figure 2 showed examples of the four time-series for a healthy subject and a patient with CAD.

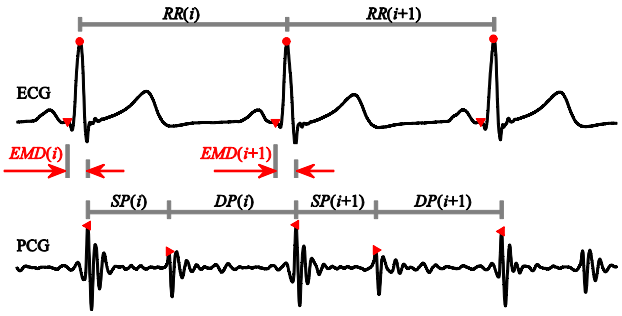

FIGURE 1. Construction of RR, SP, DP, and EMD time-series from simultaneously recorded ECG and PCG signals. The detected peaks of R-wave and the onset of QRS are marked by " ● " and "▼ ", respectively. The M1 and A2 of PCG are marked by "◄" and "► ", respectively.

C. ANALYSIS OF CARDIAC ELECTROMECHANICAL VARIABILITIES

1) TIME-DOMAIN AND FREQUENCY-DOMAIN MEASURES

In the time-domain analysis, the mean value (Mean) and standard deviation (SD) of RR, SP, DP, and EMD time-series

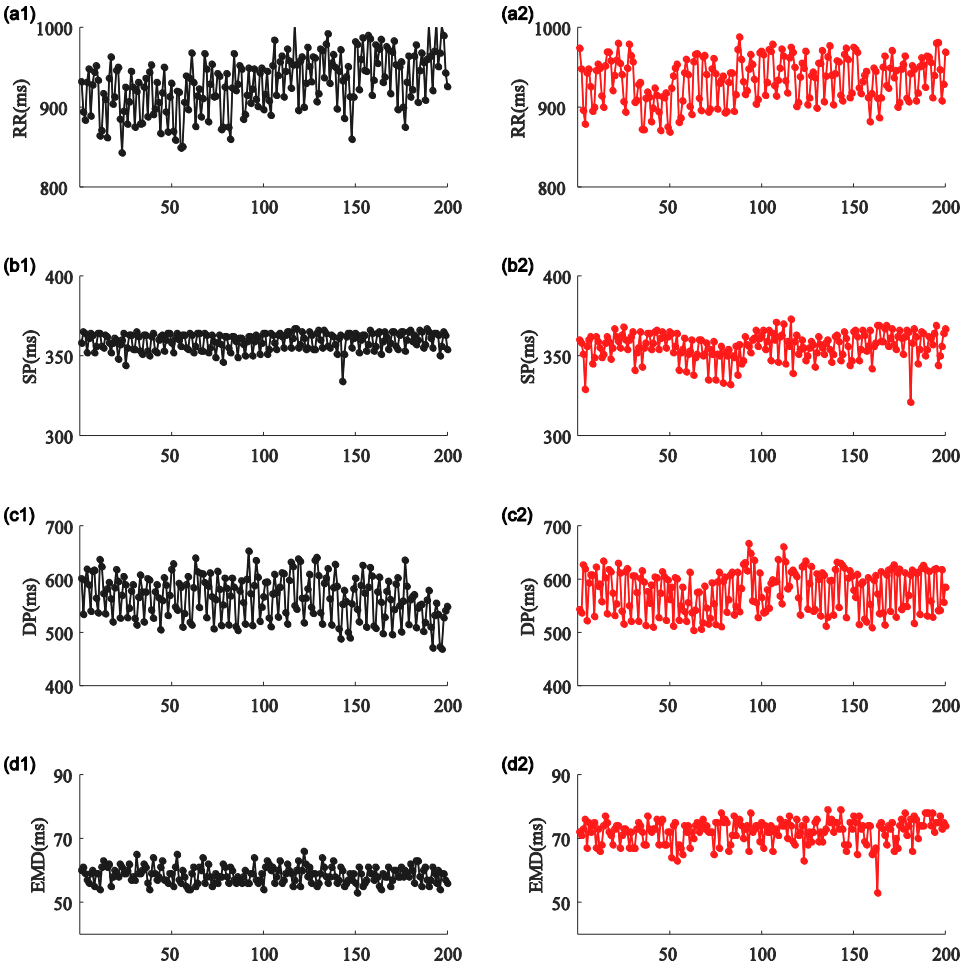

FIGURE 2. Examples of (a) RR, (b) SP, (c) DP, and (d) EMD time-series from a healthy subject (left panels) and a CAD patient (right panels). No considerable differences can be identified visually between the two subjects except that the mean level of EMD of the CAD patient is higher than that that of the healthy subject. It is not possible to draw any conclusions visually on the dynamical properties.

were calculated. Frequency-domain parameters were obtained from a 16th autoregressive model fitted using the Burg method based on previous studies [30], [31]. These parameters included normalized low- and high-frequency power (LFn, 0.04-0.15 Hz; HFn, 0.15-0.4 Hz), and LF/HF (the ratio of absolute LF power to HF power).

2) NON-LINEAR INDICES

Sample entropy (SampEn), permutation entropy (PE), and the dynamical pattern analysis were performed. Given a time-series $\{\mathbf{u}_i = u(i), 1 \le i \le N\}$, the SampEn could be calculated as follows.

a) Construct $N - m$ vectors $\{\mathbf{X}_i^m = u(i), u(i+1), \ldots, u(i+m-1), 1 \le i \le N-m\}$.

b) The distance between $\mathbf{X}_i^m$ and $\mathbf{X}_j^m$ $(j \ne i)$ is define by $d_{i,j}^m = \max\{|u(i+k) - u(j+k)|, 0 \le k \le m-1\}$.

c) For a given r, $B_i^m(r)$ is defined by

$$B_i^m(r) = \frac{\sum_{j=1, j\ne i}^{N-m} \Theta(r - d_{i,j}^m)}{N-m-1}, \quad (1)$$

wherein $\Theta(-)$ is the Heaviside function.

d) Extend dimension m to $m+1$ and calculate $B_i^{m+1}(r)$ by repeating step a) to step c).

e) SampEn can be calculated by:

$$SampEn(m, r, N) = -\ln\left(\sum_{i=1}^{N-m} B_i^{m+1}(r) \Big/ \sum_{i=1}^{N-m} B_i^m(r)\right) \quad (2)$$

We chose $m = 2$ and $r = 0.2 \times SD$ to keep in accordance with the previous studies [32], [33]. More detailed algorithms of SampEn could be found in [34]–[36].

The PE could be calculated as follows.

a) Construct $N - m + 1$ vectors $\{\mathbf{X}_i^m = u(i), u(i+1), \ldots, u(i+m-1), 1 \le i \le N-m+1\}$.

b) Construct symbolic vectors $\left\{\boldsymbol{\varphi}_i^m = (\varphi(i), \varphi(i+1), \ldots, \varphi(i+m-1))\right\}$ by coarse-graining $\mathbf{X}_i^m$ with a given Δ, that is

$$\varphi(i) = floor\left(\frac{u(i) - \min(\mathbf{X}_i^m)}{\Delta}\right) \quad (3)$$

c) Sort $\boldsymbol{\varphi}_i^m$ in ascending order to obtain ordinal patterns and then define dynamical patterns by dividing ordinal patterns into five classes, i.e., constant pattern (-P), non-increasing pattern (↘P), non-decreasing pattern (↗P), convex pattern (↘↗ P) and concave pattern (↗↘ P). The dynamical patterns in case $m = 3$ was illustrated in Fig. 3.

d) Let $\{p(D_i), 1 \le i \le 5\}$ be the probability of five dynamical patterns and PE can be calculated by:

$$PE(m, \Delta) = -\sum_i p(D_i) \ln p(D_i) \quad (4)$$

Here the combination m and Δ which demonstrated best distinguishing ability was chosen. For more information on detailed algorithms, readers can refer to [37], [38].

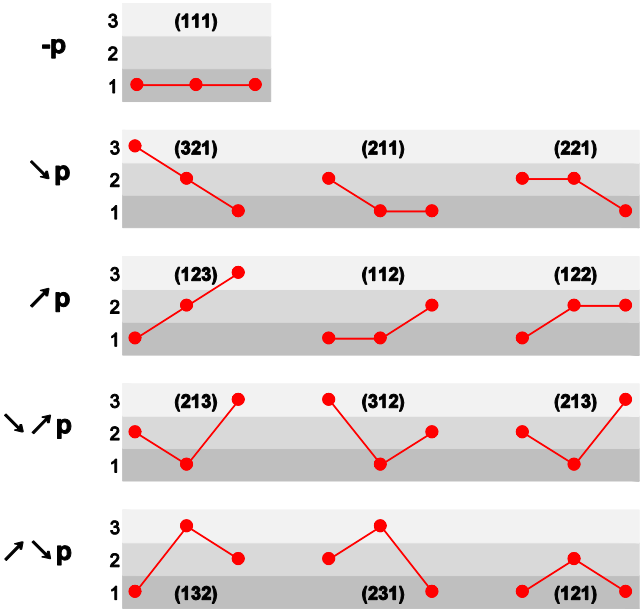

FIGURE 3. The dynamical patterns in case m = 3.

D. STATISTICAL ANALYSIS

All indices were first subjected to Kolmogorov–Smirnov test to examine the normality. Statistical difference between healthy and CAD groups was compared using the Student's t-test if a metric was normally distributed and using Mann–Whitney U test otherwise. Statistical significance was set a priori at $p < 0.05$. These statistical analyses were performed using the SPSS software (Version 20.0, IBM, USA).

TABLE 2. Original feature sets of two SVM models.

Model	Indices	Features	Number
1	HRV SPV DPV	• Mean, SD, • LFn, HFn, LF/HF, • SampEn, PE, • the probabilities of –P,↘P, ↗P, ↘↗P, and ↗↘P	36
2	HRV SPV DPV EMDV	• Mean, SD, • LFn, HFn, LF/HF, • SampEn, PE, • the probabilities of –P,↘P, ↗P, ↘↗P, and ↗↘P	48

E. CLASSIFICATION

In this section, support vector machine (SVM) [39] was adopted for the automatic classification of CAD patients and healthy control subjects. The radial basis function (RBF) was used as the kernel function, and the penalty parameter C and the kernel coefficient γ were optimized using a grid search method. As our purpose in this study was to examine whether the addition of EMDV features could improve the classification performance, we separately trained two models with 36 HRV, SPV, and DPV features included as inputs in the first model and all 48 features (36 HRV, SPV, DPV features plus 12 EMDV features) included as inputs in the second model, as specified in Table 2.

Considering potential redundancy, feature selection was implemented [40] by the following steps (assuming **S** as the original feature set containing all features):

a) The analysis of variance (ANOVA) F-values were calculated for each specific feature (i.e., using the Python function sklearn.feature_selection.f_classif), and the features were then ranked in descending order based on F values. The sorted feature set was denoted as S'.

b) Select the first feature s_i in S' and test the classification accuracy, which is denoted by A_i.

c) Choose the next feature s_{i+1} from S', and repeat the classification to get accuracy A_{i+1}. If $A_{i+1} < A_i$, delete s_{i+1}. Otherwise, maintain the feature subset.

d) Repeat step c) until exhausting all the features in S'. The final selected feature set was optimal feature subset.

The 10-fold cross-validation was used to test the generalization capability. The dataset in each group was randomly divided into 10 subsets (without overlap) with nine as training sets and one as testing set for the SVM classifier. The process was iterated 10 times so that each of the 10 subsets was used once for testing. Then the data was randomly shuffled, and the above cross validation process was repeated 10 times. The final results were obtained by averaging the performance of the 10 iterations. Sensitivity, specificity, accuracy and F1-score, as defined below were used to evaluate the model performance. The area under the receiver operating characteristic curve (AUC) was also calculated. All classification tasks were performed using Python 3.6 which was available at https://www.python.org/downloads/release/python-360/.

$$Accuracy\,(\%) = \frac{TP + TN}{TP + FP + FN + TN}, \tag{5}$$

$$Sensitivity\,(\%) = \frac{TP}{TP + FN}, \tag{6}$$

$$Specificity\,(\%) = \frac{TN}{FP + TN}, \tag{7}$$

$$F1 - score\,(\%) = \frac{2TP}{2TP + FP + FN}, \tag{8}$$

wherein TP, TN, FP and FN are the numbers of true positive, true negative, false positive, and false negative, respectively.

III. RESULTS

Eight healthy subjects and six CAD patients were excluded because of poor ECG or PCG quality. The exclusion of the 14 subjects did not introduce statistically significant differences in the basic and clinical characteristics as shown in Table 1. All results below were obtained from the remaining 46 subjects (i.e., 22 healthy subjects and 24 CAD patients).

Normal distributions of all measures were confirmed by the Kolmogorov–Smirnov test. In healthy control group, there were significant, positive correlations between SP and RR, DP and RR, as well as between SP and DP time-series (Pearson $R = 0.67, 0.98$, and 0.50 respectively, all $p < 0.01$) In CAD group, there were also significant, positive correlations in SP-RR, DP-RR, as well as SP-DP (Pearson $R = 0.73$, 0.98, and 0.59 respectively, all $p < 0.01$). No significant correlations were found in EMD with any one of the other three time-series in either group.

A. RESULTS OF TIME- AND FREQUENCY-DOMAIN MEASURES

Results for time- and frequency-domain measures of HRV, SPV, DPV, and EMDV were summarized in Fig. 4. Compared to healthy control group, the SD of SPV and the mean and SD of EMDV increased significantly in CAD group (all $p < 0.01$). No significant differences were observed in any HRV or DPV time-domain indices (all $p > 0.05$). Frequency-domain analysis did not suggest statistically significant differences between the two groups in any time-series (all $p > 0.05$).

B. RESULTS OF NON-LINEAR MEASURES

Figure 5 summarizes the results of non-linear measures. For the HRV, SPV, and DPV indices, no differences between healthy control group and CAD group were observed in SampEn, PE, or dynamical patterns (all $p > 0.05$). However, EMDV showed significantly decreased SampEn ($p < 0.05$) in CAD group compared with healthy control group. In addition, EMDV demonstrated decreased percentage of dynamical pattern $-$P ($p < 0.05$) and increased percentages of pattern $\searrow\nearrow$P ($p < 0.01$) and pattern $\nearrow\searrow$P ($p < 0.01$) in CAD group compared with healthy control group.

C. SVM RESULTS

Table 3 summarized the average performance of optimal SVM models using 10-fold cross-validation for classifying CAD patients from healthy controls. For the first SVM model (i.e., with 36 HRV, SPV and DPV indices as inputs), the optimal feature subset included mean and SD of SPV as well as SD and PE of HRV which resulted in an accuracy of 0.729, sensitivity of 0.923, specificity of 0.500, F1-score of 0.787, and AUC of 0.632. It is obvious that after including the 12 EMDV indices into the input eigenvectors (i.e., the second SVM model), the performance was improved dramatically with sensitivity increased to 0.961, specificity increased to 0.954, accuracy improved to 0.958, F1-score improved to 0.961, and AUC improved to 0.979. For this model, the optimal feature subset came out to include only EMDV indices, specifically, mean, SD and pattern $\searrow\nearrow$P and $\nearrow\searrow$P of EMDV.

IV. DISCUSSION

Physiological variabilities are gaining increasing attentions as they are quite intrinsic and useful for assessing the functioning status of the underlying control mechanisms [41]. HRV, SPV, and DPV have been intensively examined in previous studies [12],[13]. However, the variability of the time delay between the myocardial electrical and mechanical activities (i.e., EMDV) is yet to be investigated. In this study, we systematically analyzed the four cardiac electromechanical variabilities (HRV, SPV, DPV, and EMDV) in CAD

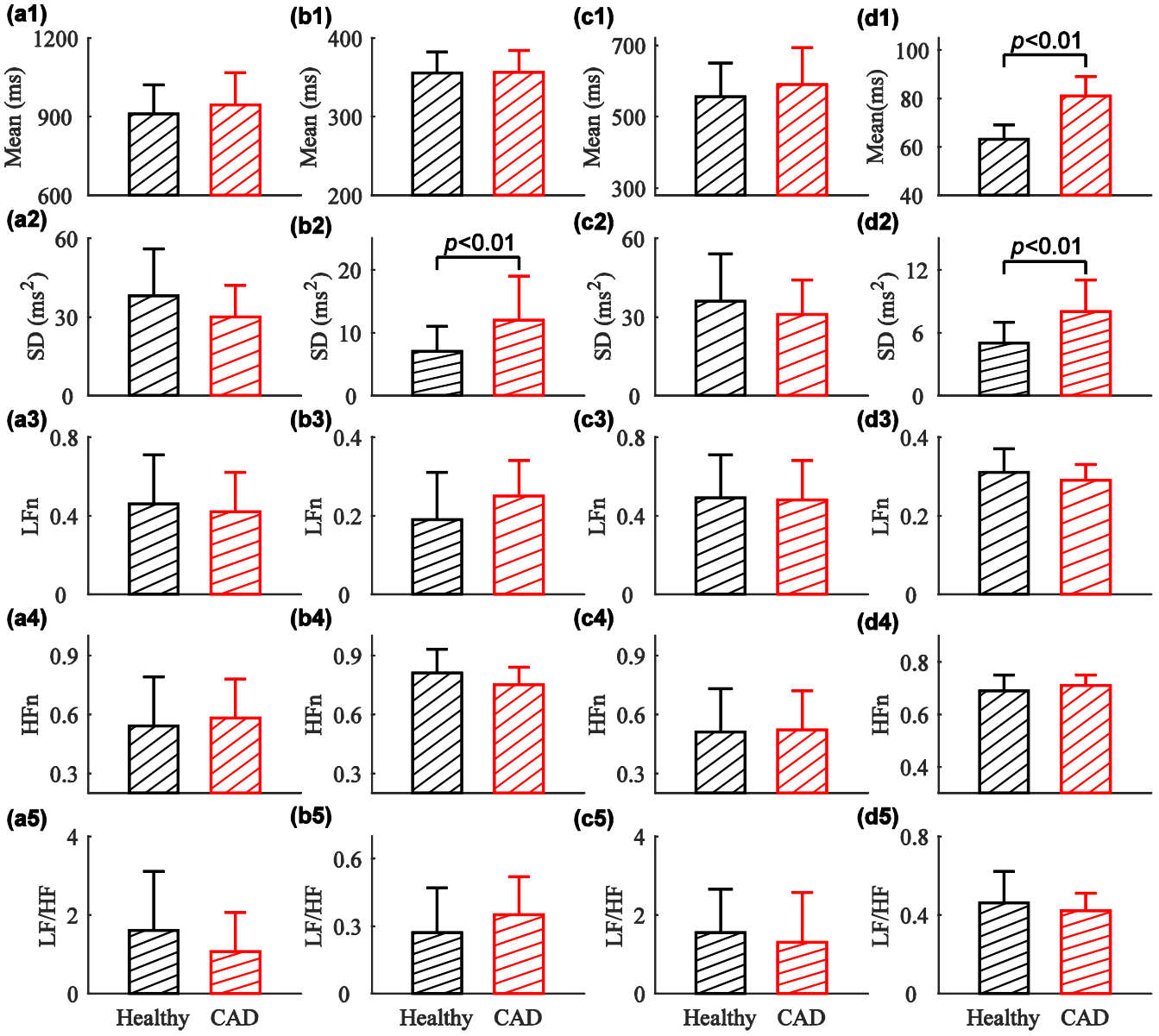

FIGURE 4. Results of time- and frequency-domain indices from (a) RR, (b) SP, (c) DP, and (d) EMD time series. Bar represents the mean and error bar the standard deviation.

patients and healthy control subjects using time-domain, frequency-domain, and nonlinear measures, aiming to test whether EMDV could provide additional information for detecting CAD.

Our results did not suggest statistical differences between CAD and healthy control groups in any of the studied HRV indices. This apparently is not consistent to some previous studies where HRV indices were shown to be able to predict CAD risk [42], and their changes were associated with the pathogenesis of coronary insufficiency and myocardial infarction [43]. Shannon entropy of HRV significantly decreased in CAD patients while no difference in SD of HRV was observed in [44]. Besides, no differences were found in mean and SD of HRV while approximate entropy decreased significantly in CAD group in [45]. We note that 24-hour HRV data have been analyzed in all the above-mentioned four studies which may lead to this discrepancy. However, results based on short-term ECG in previous studies varied. ECG recordings from 2 min to 10 min were analyzed in [42], [46]–[49]. In [46], SD and approximate entropy of HRV decreased in CAD patients whereas no difference was found in mean and LF. In [47], Shannon entropy of HRV increased significantly in CAD group while both approximate entropy and SampEn decreased significantly. In [48], [49], there were no statistical differences between CAD patients and healthy controls in any of the time-domain, frequency-domain, and entropy measures. The different study populations (i.e., the disease stages, inclusion/exclusion criteria,

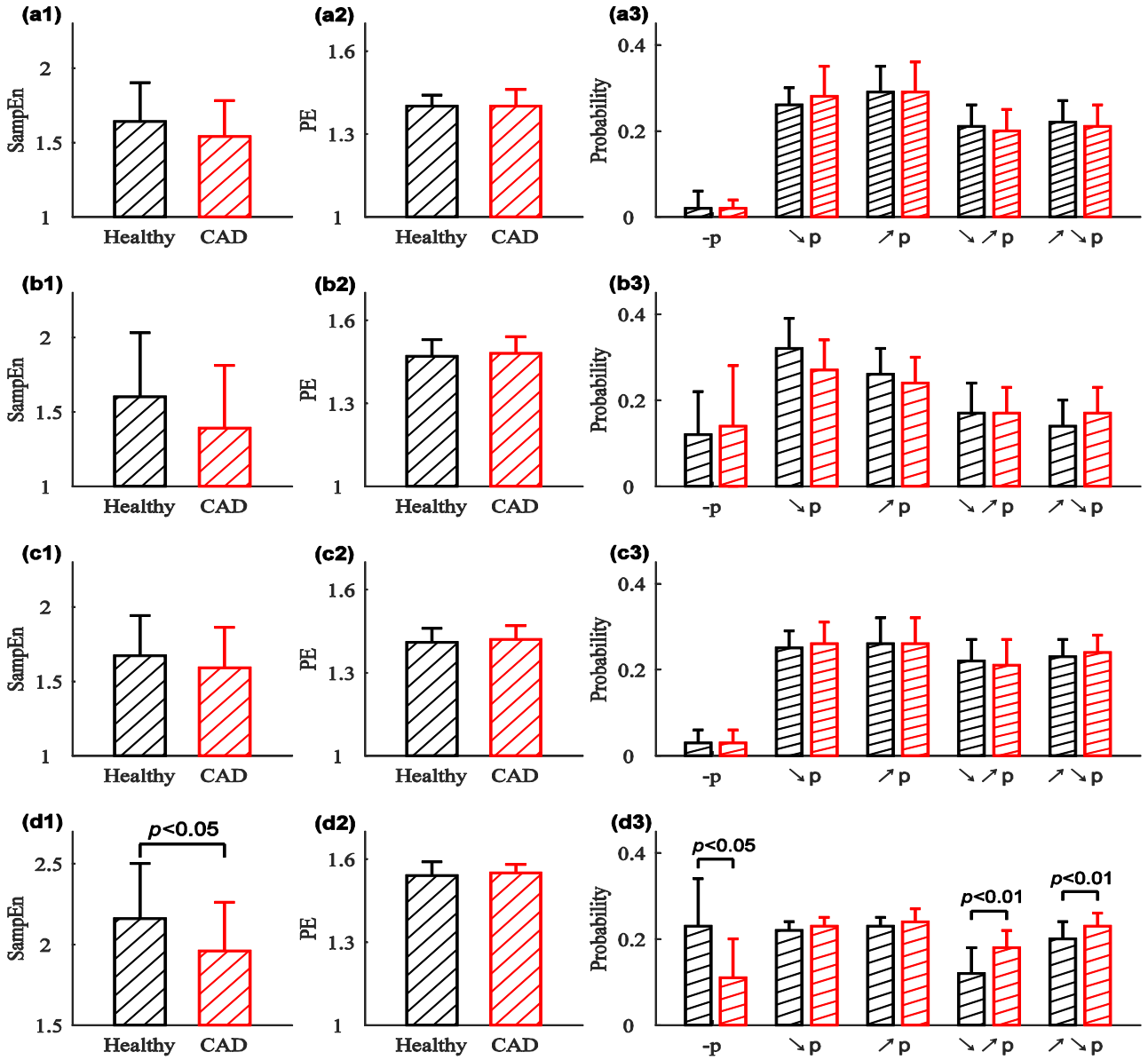

FIGURE 5. Results of sampEn, PE, and dynamical patterns distribution from (a) RR, (b) SP, (c) DP, and (d) EMD time series. Bar represents the mean levels and error bar represents the standard deviation.

age range etc.) might be one of the possible reasons that cause the discrepancies. Other possible influential factors including for example the effects of data length and measurement time etc. are to be explored.

Given the strong correlation between DPV and HRV time-series, it is not surprising that neither of the studied DPV indices showed statistical difference between the two groups. This is kind of consistent to previous concept that HRV is preferentially expressed in DPV [13]. Directly based on this concept, SPV is just the residue after taking DPV out of the HRV. But our results showed that the SD of SPV increased significantly in CAD group which indicates that SPV should not be that trivial. There does exist valuable information that is related to the cardiac function beyond HRV.

Our results also showed an increased EMDV in CAD group which is consistent with a previous study that observed prolonged EMD in patients with heart failure [10]. The atherosclerotic lesions in CAD patients causes narrowed or occlusive coronary arteries that leads to myocardial ischemia [50]. Reduced blood flow and oxygen supply to the myocardial cells result in damage to cardiac systolic function. This might be the reason why it takes more time for myocardium to start contracting after the action potential arrives. Interestingly, we also observed significant changes in the nonlinear indices of EMDV in CAD patients. Specifically, SampEn of EMDV decreased significantly in CAD patients, suggesting a loss of complexity which is in keeping with the general concept that physiological complexity decreases in diseases [51]. The impaired electromechanical conduction

TABLE 3. The average performance of 10-fold cross-validation.

Model	Accuracy	Sensitivity	Specificity	F1-score	AUC
1	0.729	0.923	0.500	0.787	0.632
2	0.958	0.961	0.954	0.961	0.979

due to the occlusive coronary artery may explain the increase instability and loss of complexity in EMDV series. Although PE did not show a significant difference, the dynamical patterns, the elements that PE algorithm takes into consideration, demonstrated significantly different distributions between the two groups with increased portions of concave ($\nearrow\searrow$P) and convex ($\searrow\nearrow$P) patterns while decreased portion of constant ($-$P) pattern in CAD patients compared to healthy control subjects. The different proportions of the five patterns signify that the dynamics of the EMD time-series may change erratically in CAD patients which is also supported by the observation that SD of EMDV increased in CAD patients. As shown in Fig 5, there are no significant differences in monotonously patterns ($\nearrow$P and $\searrow$P) between CAD and healthy groups. Therefore, the decrease of $-$P should roughly be equal to the increase of $\nearrow\searrow$P and $\searrow\nearrow$P, which leads to an unchanged PE. The dynamical patterns analysis should thus be necessary for further elucidating the intrinsic dynamics of physiological time-series in addition to the lumped entropy metrics.

Our results thus clearly point to the existing of EMDV and its physiological relevance. The unique contribution of the EMDV could further be understood from our subsequent classification analysis—the addition of EMDV features significantly improved the performance of the classification between CAD patients and healthy control subjects. The results suggest that the EMDV alteration might be sensitive and specific to CAD, which is a strong sign that EMDV is not trivial; instead, it could provide valuable additional information for evaluating the function of the heart.

There are several limitations in the current study. First, the feature points used to define the EMD time-series were labeled manually. It is time-consuming and not feasible in real applications. Automatic algorithms with rigorous validation in the context of large data sets are needed to make the analysis feasible especially for ambulatory monitoring. Second, frequency-domain features for SP, DP, and EMD time-series were all defined based on the existing definitions for HRV. Further elucidations are necessary to examine whether those components are still relevant. Third, the sample size in this study was relatively small. Further validation with larger samples is warranted. Luckily, our new human study aiming to collect a large number of CAD patients and healthy control subjects are in progress and, hopefully, these new data will be presented in future.

V. CONCLUSION

We examined for the first time the beat-to-beat variability in the cardiac electromechanical delay (i.e., EMDV) and studied its change in CAD patients compared with healthy control subjects. We observed significant changes in both the time-domain features and nonlinear metrics of EMDV in CAD patients. We further proved the unique, additional value added by the EMDV analysis in classifying CAD patients from healthy control subjects, as shown by the distinct increase of classification accuracy, sensitivity, specificity, F-1 score, and AUC compared to the classification performance based on the existing HRV, DPV, and SPV features. Our study suggests that the EMDV analysis is potentially promising in the assessment of cardiac functioning and may help with the noninvasive detection of CAD.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest to this work.

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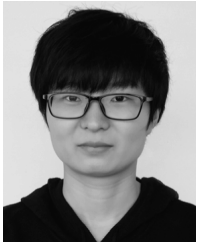

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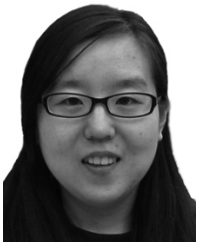

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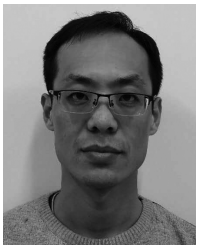

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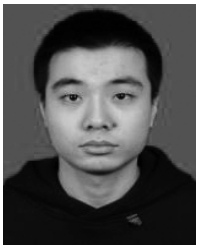

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